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Laurie Smaldone, M.D.
Senior Vice President
Worldwide Regulatory Affairs

July 19, 1999

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-0674; Proposed Draft Guidance for Industry, INDs for Phase 2 and 3 Studies of Drugs, Including Specified Therapeutic and Biotechnology-Derived Products; Chemistry, Manufacturing, and Controls Content and Format *(Federal **Register, Vol. 64,** No. 76, April 21, 1999).*

Dear Sir or Madam:

Bristol-Myers Squibb is a diversified worldwide health and personal care company with principal businesses in pharmaceuticals, consumer medicines, beauty care, nutritionals and medical devices. We are a leading company in the development of innovative therapies for cardiovascular, metabolic, oncology, infectious diseases, and neurological disorders.

The Bristol-Myers Squibb Pharmaceutical Research Institute (PRI) is a global research and development organization that employs more than 4,300 scientists worldwide. PRI scientists are dedicated to discovering and developing best in class, innovative, therapeutic and preventive agents, with a focus on ten therapeutic areas of significant medical need. Currently, the PRI pipeline comprises more than 50 compounds under active development. In 1998, pharmaceutical research and development spending totaled $1.4 billion.

For these reasons, we are very interested in and well qualified to comment on the FDA Draft Guidance for Industry regarding CMC content and format of INDs for Phase 2 and 3 Studies of Drugs.

Specific Comments

A general comment is in order regarding the subject guideline since specific comments would be too numerous and redundant in light of the December 15-17, 1997 joint AAPS/FDA workshop in which the content of the IND for the various phases of development were thoroughly reviewed and

99D-0674

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discussed. From that extensive meeting came a number of valid recommendations.

The purpose of the review was to identify what CMC information and level of detail was necessary to address the primary focus of the IND vehicle: the safety of the subjects (healthy volunteers and patients) enrolled in the various clinical trials conducted in drug development.

Unfortunately, it appears from the content of the subject draft guidance, that FDA did not take into account the considerable concerted effort and input that came out of the meeting. This is disappointing and a concern to BMS.

Attached please find a packet of presentations and recommendations that came from the various breakout sessions conducted during the AAPS/FDA meeting. It is BMS' hope that the FDA will reconsider the content of the subject draft guidance in light of the conclusions reached and recommendations proposed at the meeting.

It is our proposal that the FDA reconvene a group including AAPS,DIA and representatives from the pharmaceutical industry at large to readdress this matter before issuing the final guidance in its' current state.

The following specific comments are offered in addition to the general concern sited above.

- Lines 182-184: " Each critical quality attributes, such as identity,....., can be assessed by multiple analytical procedures,..."

  A clarification is necessary on whether multiple analytical procedures for certain quality attributes are being required of sponsors. Multiple analytical procedures will be burdensome and will generate unnecessary data which may not provide additional information to assess product safety.

  Recommendation: FDA should consider requiring multiple procedures only if the additional data will provide a better assessment of product safety.

- Lines 220 and 303: "All stability data for the clinical material used in the phase1 study should be provided."

  Recommendation: This line should be modified to "All ***relevant*** stability data..."

  The submission of only relevant data will help the agency during the review process and allow timely assessment of the filing without placing undue burden on the reviewers.

- Lines 303-304: "All available stability data for the clinical material used in phase 1 study should be provided."

A clarification on this requirement is necessary since "***all available data***" can be subject to interpretation. For example, this requirement can be interpreted to mean stability data from the phase 1 program and from clinical reassay testing. It can also mean that the agency is looking for more data in addition to that mentioned above.

- Lines 546 -548: " A detailed data table that includes the lot number, manufacturing site, ... Each table should contain data from only one storage condition. "

  Recommendation: The table data content shcuild be the main focus and the agency should allow sponsors to present data in the best table format for ease of review.

- Excessive informational details are being required in the Phase 3/pivotal study phase that do not aid in evaluating the safety of the product under investigation. All these details can be submitted in the final NDA dossier, which is typically only a few months following the completion of the phase 3 program.

  Examples of excessive requirements:

  - Lines 321 -336: The excessive information required on the drug substance characterization and description can all be reported in the NDA dossier.

  - Lines 419-421, and 522-523: Detailed information on container/closure system used for both drug substance and drug product can be part of the NDA.

BMS appreciates the opportunity to provide comment and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional pertinent information as may be requested.

Sincerely,

Laurie F. Smaldone, M. D.
Senior Vice President
Worldwide Regulatory Affairs

Attachment

Advice to facilitate expeditious product development should be distinguished from safety-related concerns explicitly.

The guidance document should focus on safety-related issues.

Product development issues can be addresses efficiently through End-of-Phase II meetings.

Explicit guidance should be issued to specify the content of the pre-meeting briefing package.

Consensus issues for IAs

Any changes in

- *Critical starting materials*
- *Effective dose*
- *Disposition/pharmacokinetics*

Deleterious changes concerning

- *Microbiological safety*
- *Novel impurities*

Analytical methods evolve with time.

- *For Phases I & II, they should be* ***qualified***

- *During Phase III, they should be* ***validated***

Sponsors should discuss stability protocol with the FDA before the end of Phase II

BUT

Need not submit stability data prior to NDA/BLA

Biopharmaceutical products may not have a defined or isolated drug substance.

The guidance should allow flexibility in analytical methods and choice of test article.

Conventional Drug Substances

Report of Breakout Session

IND CMC Philosophy

- IND filing should focus on information relevant to safety
- Later-phase discussions lay groundwork for NDA
- IND initiates FDA-Industry partnership

Development of Drug Substance

- Not linked to clinical phases
- Stage A from beginning of Development
- Stage B from preparation of batches that are critical to registration
  - » begins shortly before the CMC strategy meeting with FDA

Quality vs. Safety

- During Stage A, quality parameters defined better than safety parameters
- Must link drug substance used in tox studies to pivotal clinical batches and commercial production
- Safety becomes matter of change control

Quality vs. Safety

- **Amendments should be filed whenever a change impacts safety**

Description *and* Proof of Structure

- Identification necessary at initial IND
- Provide structure with summary of techniques used to establish structure
  - » spectra will be available upon request
- Physicochemical characterization completed during Stage B

Synthesis

	Stage A	Stage B	NDA
Start. Mat.	List	List	Acceptance criteria
Intermediate	Structure	Acceptance criteria	Acceptance criteria
Synthesis	Flow Diagram	Add description from key intermed.	Add full description
In-Process Controls	Not provided	Brief description from key intermed.	Brief description of IPCs for all steps

Specifications

- Tentative specifications developed through Stage A and Stage B
- Initial acceptance criteria in the NDA are based on safety considerations and total process experience
- Final acceptance criteria set one year after approval will include consideration of process capability

Test Methods

- Provide outline of method and validation summary during Stage A
  - » usually will include linearity, peak purity, precision, and specificity
- Complete method validation according to ICH during Stage B

Stability

- Provide a brief description of the study and analytical methods during Stage A
  - » acquire adequate data to support clinical and tox programs
- Provide description of the study to meet ICH stability requirements during Stage B

IND CMC Safety Issues

Drug Products: Parenterals and Biotechnology-derived

Guidance Section

- Change or New Information (reporting mechanism*)
  - approaches to demonstrating safety

* AR = annual report
  IN = immediate notification/amendment

1.0 Components/Composition

- Novel/non-compendial Excipient (IN)
  - full characterization
  - reference to other pharmacopoeia
  - toxicology with placebo formula
  - stability data
- Non-critical Excipient (none)

1.0 Components/Composition

Notification of Component/Composition changes depend on type of change:

- manufacturer's information
- toxicology information
- chemical/biological testing

2.0 Specifications/Methods for Components

- Change in Synthesis of Active Ingredient (IN)
  - DMF
  - GMP information
- Addition of Animal-derived Inactive Ingredient, i.e., Tween, HSA (IN)
  - Chemical/Biological Testing
  - Internal Qualification

3.0 Manufacturers

- Manufacturing Site, no historical reference (IN)
  - comparability/validation information
- Manufacturing Site, "experienced" (AR)
  - comparability/validation information
- Contract Lab (AR)
  - comparability/validation information

4.0 Method of Manufacturing and Packaging

- Equipment (none)
  - product attributes
  - GMP/qualification
- Sterilization Method, lower SAL (IN)
  - validation information

4.0 Method of Manufacturing and Packaging

- In-process Controls, no specs (AR)
  - list of tests
  - product attributes
- In-process Controls, expand limits (AR)
  - stability summary

4.0 Method of Manufacturing and Packaging

- Reprocessing, critical step (IN)
  - internal evaluation
  - product attributes

5.0 Specification and Methods

- Analytical Method, deletion (IN)
  - justification
- Analytical Method, addition (AR)
- Acceptance Limits, tightened (AR)
- Acceptance Limits, widened (IN)
  - toxicology information

5.0 Specification and Methods

- New Degradant (IN)
  - investigation of source, including comparison to toxicology retain samples
  - characterization of degradant
- Degradation Profile/Limits (IN)
  - comparability to original safety toxicity batches

6.0 Container/Closure System

- Novel System (IN)
  - dose accuracy evaluation
  - extractables data
  - stability data
- Other (AR)
  - extractables data
  - stability data

7.0 Stability

- Stress Studies (none)
  - internal evaluation (change in storage condition)
- Stability Studies (AR)
  - summary of data to support length of clinical study (i.e., no data tables)

DRUG PRODUCT - SOLIDS, LIQUIDS, MODIFIED RELEASE
Summary of Recommendations from Three Breakout Sessions

TECHNICAL SECTION	SAFETY CONCERN	RECOMMENDATION
• Component/Composition	Yes	Provide qualitative/quantitative composition on a per unit basis (Phase II & III)
Batch Formula	No	Not required (Phase II & III)
• Component Specs/Methods		
Active Ingredient	Yes	Should be covered under drug substance section - acceptance testing as proposed in guidance is a GMP issue.
Inactive Ingredient		
compendial	No	Compendial reference including USP, EP/BP, JP
non-compendial	Yes	GRAS should be acceptable. Data should be provided to support use of excipient

DRUG PRODUCT - SOLIDS, LIQUIDS, MODIFIED RELEASE

TECHNICAL SECTION	SAFETY CONCERN	RECOMMENDATION
• Method of Manufacture/ Packaging		
Product Operation	No	Phase II & III should be the same as Phase I - establishing one X only necessary in the NDA
Packaging/ Labeling Process	No	Phase III requirement should be same as Phase I/II
In-process controls	No*	Phase III should be the same as Phase I/II. *Except microbiological testing for solids in some patient populations
Reprocess procedures and controls	No	Phase III should be same as Phase I/II

DRUG PRODUCT - SOLIDS, LIQUIDS, MODIFIED RELEASE

TECHNICAL SECTION	SAFETY CONCERN	RECOMMENDATION
• Specifications/Methods Tests	Yes	Phase I wording should be the same for Phase II/III
Methods	Yes	Phase II - some appropriate validation Phase III - summary of validation rather than a full validation report
Acceptance criteria	Yes	Phase III should be same as Phase II (tentative criteria)
Degradant Profile	Yes	Degradants should be "qualified" in Phase II/III, but may not be identified until the NDA (if possible and appropriate)
Microbiology	----	Not applicable
Batch Results	No	Same requirement for Phases II & III need only provide tabular results, not COA

DRUG PRODUCT - SOLIDS, LIQUIDS, MODIFIED RELEASE

TECHNICAL SECTION	SAFETY CONCERN	RECOMMENDATION
• Container/Closure System	No	Same requirement for Phase II/III as for Phase I
• Stability		
Stress studies	No	Same requirement throughout Phase I/II/III - light stress study results should be reported in NDA
Stability studies and protocol	Yes/No	Phase II/III - submit data to support clinical use Protocol is not relevant for safety
Stability Data	Yes	Submit data on one representative batch for <u>each</u> formulation and comment on overall product stability
Analysis of Results	Yes	Provide summary conclusions of stability studies. Provide average values and ranges rather than individual data points.

Transdermals and Semisolids Breakout Session Report

Mark VanArendonk, PhD.

Pharmacia and Upjohn
December 17, 1997

Breakout Session Work Process

- CMC changes during development
- Tools for assessing safety relevance
- Reporting Mechanisms

Workshop Group

- Key Leaders
  - Wilson DeCamp
  - Mark VanArendonk
- Assistant Leaders
  - Mike Corbo
  - Amit Mitra
  - John Hunt
  - Dave Swanson
  - David Hussong
  - Vijay Tammara

CMC Changes

- 17 types of changes were identified
- 3 Primary issues which would indicate need for a safety assessment
  - Changes which would affect bioavailability/efficacy
  - Significant increases in degradation products
  - Appearance of dermal irritation

Changes Which Require Reporting

- New degradation products or significant increases from levels previously observed
- Level III Supac-SS-type changes, except site changes
- Significant change in-vitro release rate

Tools for Safety Assessments - *In Vitro*

- *In vitro* release test
- *In vitro* skin permeation
- Cytotoxicity studies
- Physical Chemical testing of formulation parameters
- Antimicrobial testing
- Analytical testing for degradants

Tools for Safety Assessments - *In Vivo*

- Irritation/Sensitization studies
- Pharmacological animal model testing
- Human bioavailability study
- Clinical bridging study

Reporting Mechanisms

- Prior notification Information Amendment, implemented immediately - ***use for safety related submissions only***
- Annual report - ***executive summary of all other development changes***
- Prepare new IND

INHALATION DOSAGE FORMS - SAFETY ISSUES

!! = Possible Safety Concern, Requires Immediate Notification

DRUG SUBSTANCE

➢ Change in particle size distribution	!!
➢ Change in physical form (powders/suspensions)	!!
➢ Impurities/OVI	If unqualified, !!
➢ Change in salt form	New IND!

INHALATION DOSAGE FORMS
- SAFETY ISSUES

!! = Possible Safety Concern, Requires Immediate Notification

CONTAINER/CLOSURE SYSTEM
(Container, valve, actuator, device, ...)

➢ Change in material	If extractables unqualified, !! If performance not comparable, !!
➢ Change in design	If performance not comparable, !!
➢ Change in supplier	If performance not comparable, !!

INHALATION DOSAGE FORMS
- SAFETY ISSUES

!! = Possible Safety Concern, Requires Immediate Notification

DRUG PRODUCT

➢ Changes in formulation - Quantitative composition	!!
- Qualitative - new excipient	!!
- change in grade	If unqualified or changes performance, !!
- drug substance	See Above.
- Pack or fill size	No
➢ Changes in manufacturing process	If performance not comparable, !!
➢ Performance (including stability)	If fails spec or not comparable, or impurities not qualified, !!

INHALATION DOSAGE FORMS
- SAFETY ISSUES

!! = Possible Safety Concern, Requires Immediate Notification

METHODS

- Changes in methods/specs — If performance not comparable or better, or impurities not qualified, !!

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